

(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 270 555 A1

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:

02.01.2003 Bulletin 2003/01

(51) Int Cl.7: C07C 315/02, C07D 401/12

(21) Application number: 01909846.6

(86) International application number:
PCT/ES01/00088

(22) Date of filing: 08.03.2001

(87) International publication number:
WO 01/068594 (20.09.2001 Gazette 2001/38)

(84) Designated Contracting States:

AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR

Designated Extension States:

AL LT LV MK RO SI

(72) Inventors:

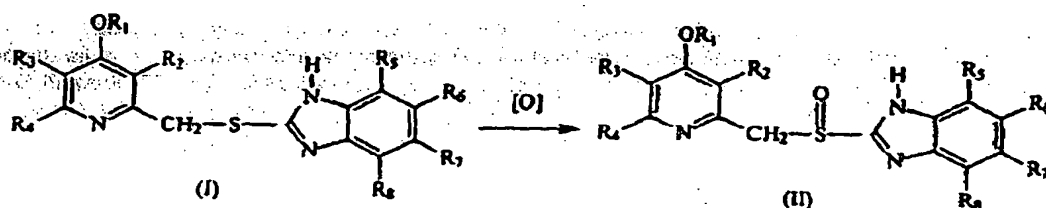
- BERENGUER MAIMO, Ramón
E-08024 Barcelona (ES)
- CAMPON PARDO, Julio
E-08024 Barcelona (ES)
- COPPI, Laura
E-08024 Barcelona (ES)

(30) Priority: 13.03.2000 ES 200000595

(71) Applicant: ESTEVE QUIMICA, S.A.
08024 Barcelona (ES)(74) Representative: Carpintero Lopez, Francisco
HERRERO & ASOCIADOS, S.L.
Alcalá, 35
28014 Madrid (ES)

(54) METHOD FOR OXIDIZING A THIOETHER GROUP INTO A SULFOXIDE GROUP

(57) The present invention relates to a procedure for the oxidation of a thioether group to a sulfoxide group, with aqueous sodium percarbonate in the presence of a molybdenum salt as a catalyst. The procedure is of application to oxidize the thioether group of a compound (I), where R_1 is a C_1 - C_6 alkyl, a halogenated C_1 - C_6 alkyl, or $-(CH_2)_n-OR_9$, where n is an integer between 1 and 6 and R_9 is H or a C_1 - C_6 alkyl; R_2 , R_3 , R_4 , R_5 , R_6 and R_8 , independently form each other represent H, a C_1 - C_6 alkyl, or C_1 - C_6 alkoxy; and R_7 is H, a C_1 - C_6 alkyl, a C_1 - C_6 alkoxy or a C_1 - C_6 fluorinated alkoxy, in order to obtain the sulfinyl derivative (II).

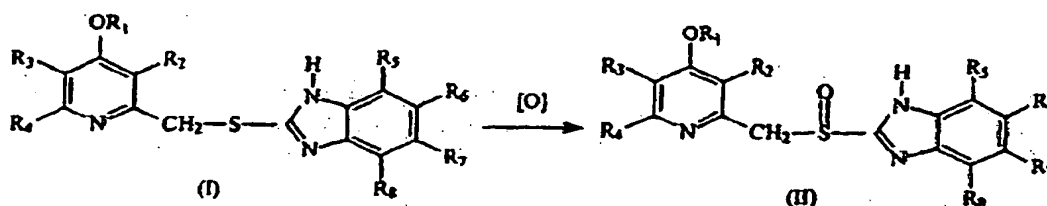


EP 1 270 555 A1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a procedure for oxidation of a thioether group to a sulfoxide group. More specifically, it relates to a procedure for oxidation of a thioether group in a compound with the formula (I) to a sulfoxide group, to obtain the sulfinyl derivative with the formula (II). IN said formulae (I) and (II), R_2 , R_3 , R_4 , R_5 , R_6 and R_8 , independently from each other represent hydrogen, an alkyl group with 1 to 6 carbon atoms, or an alkoxy group with 1 to 6 carbon atoms; R_7 represents hydrogen, an alkyl group with 1 to 6 carbon atoms, an alkoxy group with 1 to 6 carbon atoms or a fluorinated alkoxy group with 1 to 6 carbon atoms; and R_1 represents an alkyl group with 1 to 6 carbon atoms, a halogenated alkyl group with 1 to 6 carbon atoms, or a group such as $-(CH_2)_n-OR_9$, where n is an integer between 1 and 6, both



inclusive, and R_9 represents hydrogen or an alkyl group with 1 to 6 carbon atoms.

BACKGROUND OF THE INVENTION

[0002] The development of procedures for synthesizing compounds with the formula (II), particularly those meant to obtain compounds with an important therapeutic activity, such as lansoprazol, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazol, omeprazol, 2-[[[3,5-dimethyl-4-methoxy-2-pyridinyl]methyl]sulfinyl]-5-methoxy-1H-benzimidazol, rabeprazol, 2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazol, and pantoprazol, 5-difluoromethoxy-2-[[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazol, which are known as agents which inhibit gastric secretions and are administered to mammals for treating gastrointestinal ailments such as gastritis, gastric and duodenal ulcers, has been the object of many patents, without solving certain serious drawbacks related to these procedures.

[0003] In this sense are known in the state of the art several synthesis procedures for these 2-(2-pyridinylmethylsulfinyl) benzimidazols with the formula (II) which basically involve the synthesis of the precursor thioether and its subsequent oxidation to a sulfinyl group. Several procedures have been described for the synthesis of lansoprazol and related products such as that in patent EP-174726, which describes a procedure for oxidation of sulfur with one of m-chloroperoxybenzoic, peracetic, trifluoroperoxyacetic or permallic acids, sodium bromite or sodium hypochlorite, or hydrogen peroxide.

[0004] Patent application WO98/09962 describes a method for preparing omeprazol by oxidation of its thioether precursor with a peroxyacetic acid in a biphasic medium of water and a chlorinated organic solvent. Likewise, patent application WO99/25711 also describes a method for the separation of omeprazol in which the oxidation of the thioether precursor is realized with cumenyl hydroperoxide or t-butyl hydroperoxide in the presence of a titanium complex.

[0005] EP-302720 describes a procedure in which oxidation of the thioether group of compounds as 2-(2-pyridinylmethylthio) benzimidazols is achieved with hydrogen peroxide, using as catalyst vanadium pentoxide, sodium metavanadate, ammonium metavanadate or vanadium (IV) acetylacetonate.

[0006] WO98/40378 describes a procedure in which the oxidation of the thioether group of compounds as 2-(2-pyridinylmethylthio) benzimidazols is achieved by compounds of the peroxy type, such as peracids, alkylhydroperoxides, benzoylperoxides, hydrogen peroxide, metaperiodates and tetraalkylammonium perborates, etc., and as catalyst are used vanadium compounds.

[0007] Patent application WO99/0252 describes a method for oxidation of thioether to sulfoxide based on the use of a peroxoborate salt in the presence of an anhydride acid or a metal catalyst, or with an N-halosuccinimide, 1,3-dihalo-5,5-dimethylhydantoin or a salt of dichloroisocyanuric acid in the presence of a base.

[0008] Patent ES-2105953 describes the conditions for oxidation of thioether to sulfoxide based on the use of hydrogen peroxide in a medium of sodium bicarbonate, catalyzed by phosphotungstic acid $H_3(P(W_3O_{10})_4) \cdot xH_2O$.

[0009] Patent ES-2060541 describes a procedure for oxidation of sulfur to sulfoxide with potassium peroxy monosulfate, with or without the presence of a ketone, or with hydrogen peroxide, in the presence of catalysts of Mo and V

acetylacetonate.

[0010] Another patent which describes the oxidation of sulfur to sulfoxide with t-butyl hydroperoxide catalyzed by vanadium is ES-2063705, in this case for the synthesis of lansoprazol.

[0011] Patent US-5374730 describes an oxidation stage of sulfur to sulfoxide with hydrogen peroxide and catalyzed by vanadium acetylacetonate.

[0012] Patent ES-2036948 describes a procedure for the synthesis of lansoprazol, in which the last stage involves the oxidation of the thioether precursor of lansoprazol to sulfoxide, with m-chloroperbenzoic acid or magnesium monoperoxyphthalate in the presence of a quaternary ammonium salt, or hydrogen peroxide, with a W or molybdenum catalyst.

[0013] From the state of the art it is inferred that the procedure which has been developed farthest and is more widely used for oxidation is that which employs vanadium catalysts. Among these basic procedures the most efficient is the one which uses hydrogen peroxide and vanadium catalyst; and the one which uses magnesium monoperoxyphthalate (MMPP), as described in patent EP-533264. Despite this, there are unsolved drawbacks in these procedures such as the fact that vanadium compounds are relatively toxic, and that MMPP is expensive to use industrially, as well as generating phthalic acid as a reaction byproduct. Finally, in both cases sulfone and N-oxide are produced as impurities due to overoxidation. Production of these impurities obviously results in increased costs in the procedures for obtaining any of these products.

[0014] The procedure described for oxidation of the thioether precursor of lansoprazol involving the use of hydrogen peroxide and molybdenum catalysts also does not give good results as it has the drawback of producing a large amount of sulfone and some N-oxide as undesirable byproducts.

[0015] The need therefore exists to develop an improved procedure for the oxidation of these thioethers to sulfoxide, and in particular applicable to synthesis of omeprazol, lansoprazol, rabeprazol and pantoprazol, or their precursors.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The present invention relates to a procedure for oxidation of a thioether group to a sulfoxide group, and in particular for oxidation of a thioether group of a compound with the formula (I) as defined above, to a sulfinyl derivative with the formula (II).

[0017] In the sense used in this description, the term "halogenated alkyl group with 1 to 6 carbon atoms" signifies an alkyl group with 1 to 6 carbon atoms which contains one or more halogen atoms, preferably fluorine or chlorine, substituting one or more hydrogen atoms. Similarly, the term "fluorinated alkoxy group with 1 to 6 carbon atoms" signifies an alkoxy group with 1 to 6 carbon atoms which contains one or more fluorine atoms substituting one or more hydrogen atoms, such as 2,2,2-trifluoroethoxy or difluoromethoxy.

[0018] The procedure involves the oxidation of the thioether with sodium percarbonate in the presence of a molybdenum salt as a catalyst, which is preferably ammonium molybdate. This new procedure has proved to be more efficient than the various procedures described in the discussion on the state of the art. Additionally, sodium percarbonate stands out as an oxidizing agent which is easy to handle, relatively stable and simple to store.

[0019] The procedure of the present invention presents a number of improvements on the previous procedures, such as the following:

- the reagents used are commercially affordable,
- molybdenum catalysts are less toxic than vanadium catalysts,
- the pH of the reaction mixture is slightly basic and thus adequate for stability of compounds such as lansoprazol in a solution,
- the formation of N-oxide as an impurity is unappreciable or appreciable at negligible amounts,
- the percentage of sulfone produced is low,
- the oxidized product can be isolated by precipitation in the reaction medium,
- a first purification of the sample can be performed by a fractionated precipitation at a controlled pH.

[0020] In addition, the oxidation was attempted with vanadium catalysts, but the results obtained were not satisfactory.

[0021] In a preferred realization of the procedure of the invention the oxidation is effected with a molar ratio of sodium percarbonate to the thioether with the formula (I) ranging between 0.5 and 1.4, and preferably between 0.6 and 1.2.

[0022] The amount of catalyst (molybdenum salt) employed is between 0.3% and 7%, and preferably between 0.5% and 5%, by weight, with respect to the thioether with formula (I).

[0023] The solvent used for the oxidation reaction is an alcohol with a low molecular mass, preferably methanol.

[0024] The reaction temperature is between -10°C and 25°C, preferably between -5°C and 20°C.

[0025] Among the compounds with the formula (II) are lansoprazol, omeprazol, rabeprazol, pantoprazol and

2-[[[4-(3-hydroxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1*H*-benzimidazol, which may be obtained from the corresponding thioether precursors by oxidation of the thioether group to a sulfoxide group according to the procedure provided by this invention. In a particular realization, said compounds with formula (II) are obtained by oxidation of the thioether group present in the thioether precursors with the corresponding formula (I) to sulfoxide, in methanol (solvent) with sodium percarbonate, in a molar ratio with respect to the initial thioether ranging between 0.6 and 1.2, in the presence of ammonium molybdate (catalyst) with a ratio of ammonium molybdate with respect to the initial thioether between 0.5% and 5% by weight, and at a temperature between -5°C and 20°C.

[0026] 2-[[[4-(3-hydroxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1*H*-benzimidazol may be used as a material for the synthesis of rabeprazol by the transformation of the hydroxyl group into a methoxy group.

[0027] The following examples are provided for purposes of illustration only and should not be understood as a definition of the limits of the invention.

EXAMPLE 1

Preparation of lansoprazol

[0028] 10 g of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1*H*-benzimidazol were dissolved in 50 ml of methanol and 0.3 g of ammonium molybdate were added. The solution was cooled to 10°C, and 3.35 g of sodium percarbonate added slowly, kept stirred at the same temperature for 15 hours. After the reaction ended 250 ml of water were added and the pH of the resulting mixture adjusted to 10 with 10% acetic acid. This was kept stirred for 1 hour and the solid obtained was filtered, and subsequently washed with water and dried in a vacuum oven at 40°C. This provided 9.4 g of lansoprazol (yield: 90%).

EXAMPLE 2

Preparation of omeprazol

[0029] 30 g of 2-[[[3,5-dimethyl-4-methoxy-2-pyridinyl]methyl]sulfinyl]-5-methoxy-1*H*-benzimidazol were dissolved in 150 ml of methanol and 0.9 g of ammonium molybdate were added. The solution was cooled to 10°C and 11.7 g of sodium percarbonate were added slowly and kept at this temperature for 15 hours, after which 450 ml of water were added slowly and the pH adjusted to 8.6 with 10% acetic acid. The resulting solid was filtered and then washed with water and acetone. After drying in a vacuum oven at 30/35°C, 25.4 g of omeprazol were obtained (yield: 81%).

EXAMPLE 3

Preparation of rabeprazol

[0030] 2.3 g of 2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridinyl]methyl]thio]-1*H*-benzimidazol were dissolved in 11.5 ml of methanol and 90 mg of ammonium molybdate were added. The solution was cooled to 5°C and 0.87 g of sodium percarbonate were added, then kept stirred at this temperature for 6 h. After the reaction finished 22 ml of water were added, then heating to 20°C and adjusting the pH of the mixture to 7.5 with acetic acid. The mixture is extracted with 50 ml of dichloromethane and the organic phase was separated, which was then washed with 100 ml of water. The solvent was evaporated at a reduced pressure. 2.0 g of rabeprazol were obtained (yield: 81%).

EXAMPLE 4

Preparation of pantoprazol

[0031] 310 mg of 5-difluoromethoxy-2-[[[3,4-dimethoxy-2-pyridinyl]methyl]thio]-1*H*-benzimidazol were dissolved in 1.5 ml of methanol and 12 mg of ammonium molybdate added. The solution was cooled to 5°C and 0.11 g of sodium percarbonate were added, then kept stirred at the same temperature for 4 h. After the reaction ended 3 ml of water were added, then heating to 20°C and adjusting the mixture of the pH to 7.5 with acetic acid. The mixture is extracted with 5 ml of dichloromethane and the organic phase separated, then washed with 10 ml of water. The solvent was evaporated at a reduced pressure. 274 mg of pantoprazol were obtained (yield: 88%).

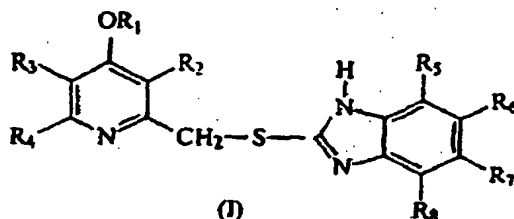
EXAMPLE 5

Preparation of 2-[[3-methyl-4-(3-hydroxypropoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazol

2.2 g of 2-[[[4-(3-hydroxypropoxy)-3-methyl-2-pyridinyl]methyl]thio]-1H-benzimidazol were dissolved in 11.5 ml of methanol and 90 mg of ammonium molybdate were added. The solution was cooled to 5°C and 0.87 g of sodium percarbonate were added, then stirring at the same temperature for 6 h. After the reaction ended 22 ml of water were added, then heating to 20°C and adjusting the pH of the mixture to 7.5 with acetic acid. The mixture was extracted with 150 ml of dichloromethane and the organic phase separated. The solvent was evaporated at reduced pressure, providing 2.0 g of 2-[[[4-(3-hydroxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazol (yield: 86%).

Claims

1. Procedure for oxidation of a thioether group to a sulfoxide group, **characterized in that** the oxidation of the thioether group is effected with sodium percarbonate and a catalyst consisting of a molybdenum salt.
2. Procedure as claimed in claim 1, **characterized in that** the product which is oxidized is a 2-(2-pyridinylmethyl-thio)benzimidazol with formula (I)



where

R₁ represents an alkyl group with 1 to 6 carbon atoms, a halogenated alkyl group with 1 to 6 carbon atoms or a -(CH₂)_n-OR₉ group, where n is an integer between 1 and 6, both inclusive, and R₉ represents hydrogen or an alkyl group with 1 to 6 carbon atoms;

R₂, R₃, R₄, R₅, R₆ and R₈, independently from each other represent hydrogen, an alkyl group with 1 to 6 carbon atoms or an alkoxy group with 1 to 6 carbon atoms; and

R₇ represents hydrogen, an alkyl group with 1 to 6 carbon atoms, an alkoxy group with 1 to 6 carbon atoms or a fluorinated alkoxy group with 1 to 6 carbon atoms.

3. Procedure as claimed in claim 1 or 2, **characterized in that** the molybdenum salt is ammonium molybdate.
4. Procedure as claimed in claim 1, **characterized in that** the ratio of the molybdenum salt with respect to the thioether is between 0.3% and 7% by weight.
5. Procedure as claimed in claim 4, **characterized in that** the ratio of the molybdenum salt is between 0.5% and 5% by weight with respect to the thioether.
6. Procedure as claimed in claim 1, **characterized in that** the molar ratio of sodium percarbonate to thioether is between 0.5 and 1.4.
7. Procedure as claimed in claim 6, **characterized in that** the molar ratio of sodium percarbonate to thioether is between 0.6 and 1.2.
8. Procedure as claimed in claim 1, **characterized in that** the reaction temperature is between -10°C and 25°C.

9. Procedure as claimed in claim 8, **characterized in that** the reaction temperature is between -5°C and 20°C.
10. Procedure as claimed in claim 1, **characterized in that** the solvent is an alcohol with a low molecular mass.
- 5 11. Procedure as claimed in claim 10, **characterized in that** the alcohol of low molecular mass is methanol.
12. Procedure for preparation of lansoprazol **characterized in that** the last stage of the synthesis is achieved by the oxidation of the thioether precursor according to any of claims 1 to 11.
- 10 13. Procedure for preparation of lansoprazol according to claim 12, **characterized in that** the oxidation of the thioether group of the 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazol to a sulfoxide group takes place in methanol as solvent, using sodium percarbonate in a molar ratio with respect to the initial thioether between 0.6 and 1.2, and ammonium molybdate as a catalyst, with a ratio of ammonium molybdate ranging between 0.5% and 5% by weight with respect to the thioether, and at a reaction temperature between -5°C and 20°C.
- 15 14. Procedure for preparation of omeprazol **characterized in that** the last stage of the synthesis is achieved by the oxidation of the thioether precursor according to any of claims 1 to 11.
- 20 15. Procedure for preparation of omeprazol according to claim 14, **characterized in that** the oxidation of the thioether group of the 2-[[[3,5-dimethyl-4-methoxy-2-pyridinyl]methyl]sulfinyl]-5-methoxy-1H-benzimidazol to a sulfoxide group takes place in methanol as solvent, using sodium percarbonate in a molar ratio with respect to the initial thioether between 0.6 and 1.2, and ammonium molybdate as a catalyst, with a ratio of ammonium molybdate ranging between 0.5% and 5% by weight with respect to the thioether, and at a reaction temperature between -5°C and 20°C.
- 25 16. Procedure for preparation of rabeprazol **characterized in that** the last stage of the synthesis is achieved by the oxidation of the thioether precursor according to any of claims 1 to 11.
- 30 17. Procedure for preparation of rabeprazol according to claim 16, **characterized in that** the oxidation of the thioether group of the 2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazol to sulfoxide takes place in methanol as a solvent, using sodium percarbonate in a molar ratio with respect to the initial thioether between 0.6 and 1.2, and ammonium molybdate as a catalyst, with a ratio of ammonium molybdate ranging between 0.5% and 5% by weight with respect to the thioether, and at a reaction temperature between -5°C and 20°C.
- 35 18. Procedure for preparation of pantoprazol **characterized in that** the last stage of the synthesis is achieved by the oxidation of the thioether precursor according to any of claims 1 to 11.
- 40 19. Procedure for preparation of pantoprazol according to claim 18, **characterized in that** the oxidation of the thioether group of the 5-difluoromethoxy-2-[[[3,4-dimethoxy-2-pyridinyl]methyl]thio]-1H-benzimidazol to sulfoxide takes place in methanol as a solvent, using sodium percarbonate in a molar ratio with respect to the initial thioether between 0.6 and 1.2, and ammonium molybdate as a catalyst, with a ratio of ammonium molybdate ranging between 0.5% and 5% by weight with respect to the thioether, and at a reaction temperature between -5°C and 20°C.
- 45 20. Procedure for preparation of 2-[[[3-methyl-4-(3-hydroxypropoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazol **characterized in that** the last stage of the synthesis is achieved by the oxidation of the thioether precursor according to any of claims 1 to 11.
- 50 21. Procedure for preparation of 2-[[[3-methyl-4-(3-hydroxypropoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazol according to claim 20, **characterized in that** the oxidation of the thioether group of the 2-[[[3-methyl-4-(3-hydroxypropoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazol to sulfoxide takes place in methanol as a solvent, using sodium percarbonate in a molar ratio with respect to the initial thioether between 0.6 and 1.2, and ammonium molybdate as a catalyst, with a ratio of ammonium molybdate ranging between 0.5% and 5% by weight with respect to the thioether, and at a reaction temperature between -5°C and 20°C.

INTERNATIONAL SEARCH REPORT

International application No
PCT/ES 01/00088

A. CLASSIFICATION OF SUBJECT MATTER IPC7 C07C 315/02, C07D 401/12 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched IPC7 C07C, C07D, A61K Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPODOC, WPI, REGISTRY, CAPLUS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y X	ES-2036948-A (CENTRO GENESIS PARA LA INVESTIGACION, S.L.) 01.06.1993, page 12, lines 37-42, page 14, lines 56-59, page 15, lines 5-12, revendications 33,34, example 17.	1-21 12,13
Y X	ES-2026761-A (CENTRO GENEIS PARA LA INVESTIGACION, S.L.) 01 May 1992 (01.05.92), page 22, lines 17-21, revendications 50 and 51, examples 32 and 33	1-21 14,15
P,Y	EP-997461-A (EISAI CO., LTD.) 03 May 2000, revendications 1-6, 11-13	1-21
Y A	M.Madescalaire, "Synthesis of sulfoxides by oxidation of thioethers" Tetrahedron, 1986, Vol. 42, N° 20, pages 5459-5495. Apartados 2.1 and 2.3	1 3-11
Y A	J.Muyart, "Sodium perborate and sodium percarbonate in organic synthesis". Synthesis, 1995, Vol. 11, pages 1325-1347	1 3-11
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents: "A" document defining the general state of the art, which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 28 June 2001 (20.06.2001)		Date of mailing of the international search report 05 July 2001 (05.07.2001)
Name and mailing address of the ISA/ ES S.P.T.O.		Authorized officer E.DAVILA MURO Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No
PCT/ES 01/00088

C. (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. McKillop, W.R. Sanderson, "Sodium oerborate and sodium percarbonate: Cheap, safe and versatile oxidising agents for organic synthesis". Tetrahedron, 1995, Vol. 51, No 22, pages 6145-6166.	1, 3-11
A	ES-2060541-A (LABORATORIOS VINAS, S.A.) 16 November 1994, page 5, lines 26-39, 55-62, page 6, lines 1-5	2, 12-21
A	CA-2254597-A (BAYER CORP.) 12 June 1999 (12.06.99) Page 2, lines 15-27, revendications 10-12	1, 6-11
A	Maignien, S.Ait-Mohand, J. Muyart, "A practical Molybdenum-catalyzed oxidation of alcohols by sodium percarbonate". Synlett, 1996, Vol. 5,	1, 3-11

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No
PCT/ES 01/00088

Patent document Cited in search report	Publication Date	Patent family Member (s)	Publication date
ES 2036948 A	01.09.1994	SI 9200336 A ES 2058027 A HR 921309 A ES 2066701 A,B ES 2067407 A,B ES 2105953 A,B	30.06.1993 16.10.1994 28.02.1995 01.03.1995 16.03.1995 16.10.1997
ES 2026761A	01.05.1992	EP 484265 A	06.05.1992
EP 997461 A	03.05.2000	WO 9902521 A JP 11071371 A JP 11171884 A JP 2000016992 A CN 1267295 T	21.01.1999 16.03.1999 29.06.1999 18.01.2000 20.09.2000
EP 2060541 A	16.11.1994	NONE	01.10.1999
CA 2254597 A	12.06.1999	MX 9810188 A	

Form PCT/ISA/210 (continuation of second sheet) (July 1998)